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09/852,976	05/10/2001	Tse W. Chang	THI-001	4934
959	7590	12/03/2003	EXAMINER	
LAHIVE & COCKFIELD, LLP. 28 STATE STREET BOSTON, MA 02109			HUYNH, PHUONG N	
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			1644	

DATE MAILED: 12/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/852,976	CHANG ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE Three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 August 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 3, 4, 14-17, 19, 20, 23, 26, 27, 30, 39, 40 and 60-68 is/are pending in the application.
- 4a) Of the above claim(s) 23, 63, 64 and 66 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 3-4, 14-17, 19-20, 26, 27, 30, 39-40, 60-62, 65, 67 and 68 is/are rejected.
- 7) ☒ Claim(s) 17 and 67 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Claims 3-4, 14-17, 19-20, 23, 26-27, 30, 39-40, and 60-68 are pending.
2. Newly submitted claim 63-64, and 66 directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The immunogenic composition wherein the polypeptide of molecule such as the ones recited in said claims differ with respect to their structures as compared to CD79 α , CD79 β . Further, the said molecules are not specifically expressed on the surface of activated B cells. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim [3] withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.
3. Claims 23, 63-64, and 66 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.
4. Claims 3-4, 14-17, 19-20, 26, 27, 30, 39-40, 60-62, 65, 67 and 68 drawn to an immunogenic composition comprising a first polypeptide coupled to a second polypeptide wherein the first autologous polypeptide to a subject that read on the species of CD79 α (Ig α), CD79 β and Ig and wherein the second heterologous polypeptide that read on IgG Fc are being acted upon in this Office Action.
5. The following new grounds of objection and rejections are necessitated by the amendment filed 8/22/03.
6. Claims 17, and 67 are objected to for reciting non-elected embodiment.
7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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8. Claims 3-4, 14-17, 19-20, 26, 27, 30, 39-40, 60-62, 65, 67 and 68 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) an immunogenic composition comprising a first polypeptide which is autologous to a subject, coupled to a second polypeptide, which is heterologous to the subject, wherein the first polypeptide specifically expressed on the surface of activated B cells selected from the group consisting of CD79 α , CD79 β , and CD20, and wherein the second polypeptide is the Fc fragment of Ig heterologous to a subject and contains at least one T helper cell epitope, the composition being capable of eliciting an antibody immune response against B cells in the subject, (2) the said composition wherein the first polypeptide is a human and the subject is a human, (3) The said composition wherein the first polypeptide and the second polypeptide are expressed as a fusion protein, (4) The said composition wherein the fusion protein is dimeric, (5) The said composition wherein the first polypeptide and the second polypeptide are coupled via a chemical linkage for eliciting autoantibodies against said autologous antigen expressed on the B cell of the subject, **does not** reasonably provide enablement for:

(1) *any* immunogenic composition comprising *any* “first polypeptide” which is autologous to any subject or which is immunologically cross-reactive with the autologous polypeptide coupled to *any* “second polypeptide”, which is heterologous to the subject, wherein the first polypeptide comprises any immunogenic portion of any polypeptide specifically expressed on the surface of activated B cells and wherein the second polypeptide contains at least one T helper cell epitope, the composition being capable of eliciting any immune response against B cells in the subject,

(2) the immunogenic composition comprising *any* “first human polypeptide” which is autologous to the human subject or which is immunologically cross-reactive with the autologous polypeptide coupled to *any* “second polypeptide”, which is heterologous to the subject, wherein the first polypeptide comprises any immunogenic portion of any polypeptide specifically expressed on the surface of activated B cells and wherein the second polypeptide contains at least one T helper cell epitope, the composition being capable of eliciting any immune response against B cells in the subject,

(3) the immunogenic composition comprising *any* “first polypeptide” which is autologous to any subject or which is immunologically cross-reactive with the autologous polypeptide coupled to *any* “second polypeptide”, which is heterologous to the subject, wherein the first polypeptide comprises any immunogenic portion of any polypeptide specifically expressed on the

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surface of activated B cells and wherein the second polypeptide contains at least one T helper cell epitope, the composition being capable of eliciting any immune response against B cells in the subject wherein the first polypeptide and the second polypeptide are expressed as a fusion protein,

(4) The said immunogenic composition wherein the fusion protein is dimeric,

(5) The immunogenic composition comprising *any* “first polypeptide” which is autologous to any subject or which is immunologically cross-reactive with the autologous polypeptide coupled via a chemical linkage to *any* “second polypeptide”, which is heterologous to the subject, wherein the first polypeptide comprises any immunogenic portion of any polypeptide specifically expressed on the surface of activated B cells and wherein the second polypeptide contains at least one T helper cell epitope, the composition being capable of eliciting any immune response against B cells in the subject,

(6) *any* immunogenic composition comprising: a first polypeptide which is autologous to *any* subject or which is immunologically cross-reactive with the autologous polypeptide coupled to any second polypeptide which is which is heterologous to the subject, wherein the first polypeptide comprises any “immunogenic portion” of a molecule selected from the group consisting of: CD79 α , CD79 β , and CD20 and wherein the second polypeptide comprises at least one T cell epitope, the composition being capable of eliciting any immune response against B cells in the subject,

(7) The composition comprising: a first human polypeptide which is autologous to human subject or which is immunologically cross-reactive with the autologous polypeptide coupled to any second polypeptide which is which is heterologous to the subject, wherein the first polypeptide comprises any “immunogenic portion” of a molecule selected from the group consisting of: CD79 α , CD79 β , and CD20 and wherein the second polypeptide comprises at least one T cell epitope, the composition being capable of eliciting any immune response against B cells in the subject,

(8) the composition comprising: a first human polypeptide which is autologous to human subject or which is immunologically cross-reactive with the autologous polypeptide coupled to any second polypeptide which is which is heterologous to the subject, wherein the first polypeptide comprises any “immunogenic portion” of a molecule selected from the group consisting of: CD79 α , CD79 β , and CD20 and wherein the second polypeptide comprises at least one T cell epitope, the composition being capable of eliciting any immune response against B

cells in the subject wherein the first polypeptide and the second polypeptide are expressed as a fusion protein, a dimeric fusion protein, or coupled via a chemical linkage,

(9) the immunogenic compositions mentioned wherein the second polypeptide comprises at least a portion of an Fc region of an immunogenic molecule,

(10) *Any* immunogenic composition comprising any first polypeptide which is heterologous to any subject or which is immunologically cross-reactive with any autologous polypeptide to the subject coupled to any second polypeptide which is heterologous to the subject, wherein the first polypeptide comprises any immunogenic portion of any polypeptide specifically expressed on the surface of cells targeted for elimination or reduction and the second polypeptide comprises at least one T cell epitope and wherein the composition is capable of reducing or eliminating the cells expressing the cell surface receptor,

(11) The immunogenic composition comprising any first polypeptide which is heterologous to any subject or which is immunologically cross-reactive with any autologous polypeptide to the subject coupled to any second polypeptide which is heterologous to the subject, wherein the first polypeptide comprises any immunogenic portion of any polypeptide specifically expressed on the surface of cells targeted for elimination or reduction and the second polypeptide comprises at least one T cell epitope and wherein the composition is capable of reducing or eliminating the cells expressing the cell surface receptor wherein the first and the second polypeptides are expressed as a fusion protein or a dimeric fusion protein,

(12) The immunogenic composition comprising any first polypeptide which is heterologous to any subject or which is immunologically cross-reactive with any autologous polypeptide to the subject coupled to any second polypeptide which is heterologous to the subject, wherein the first polypeptide comprises any immunogenic portion of any polypeptide specifically expressed on the surface of cells targeted for elimination or reduction and the second polypeptide comprises at least one T cell epitope and wherein the composition is capable of reducing or eliminating the cells expressing the cell surface receptor wherein the second polypeptide comprises at least a portion of an Fc region of an immunoglobulin molecule,

(13) Any immunogenic composition comprising a first polypeptide which is autologous to any subject or which is immunologically cross-reactive with any autologous polypeptide coupled to any second polypeptide which is heterologous to the subject, wherein the first polypeptide comprises an immunogenic "portion" of any cell surface polypeptide specifically expressed on the surface of B cells and any second polypeptide comprises at least one T helper

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cell epitope, the composition being capable of eliciting any immune response against B cells in the subject,

(14) The immunogenic composition comprising a first polypeptide which is autologous to any subject or which is immunologically cross-reactive with any autologous polypeptide coupled to any second polypeptide which is heterologous to the subject, wherein the first polypeptide comprises an immunogenic "portion" of any cell surface polypeptide specifically expressed on the surface of B cells and any second polypeptide comprises at least one T helper cell epitope, the composition being capable of eliciting any immune response against B cells in the subject wherein the portion of non-human immunoglobulin molecule is derived from the Fc portion of the immunoglobulin,

(15) the immunogenic composition comprising a first polypeptide which is autologous to any subject or which is immunologically cross-reactive with any autologous polypeptide coupled to any second polypeptide which is heterologous to the subject, wherein the first polypeptide comprises an immunogenic "portion" of any cell surface polypeptide specifically expressed on the surface of B cells and any second polypeptide comprises at least one T helper cell epitope, the composition being capable of eliciting any immune response against B cells in the subject wherein the first polypeptide comprises the extracellular domain of any cell surface polypeptide,

(16) The compositions mentioned above wherein the number or concentration of cells expressing the polypeptide in the subject is reduced by at least about 35-40% or 50% relative to the number or concentration of cells prior to treatment or in an untreated subject, and

(17) the immunogenic composition mentioned above wherein the composition further comprises an adjuvant for treating any disease such as cancer and autoimmune disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

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The specification discloses only four fusion proteins selected from the group consisting of (1) mouse Ig β fused to human IgG Fc, (2) CD79 α fused to the Fc region of IgG1 and (3) CD79 β fused to fused to the Fc region of IgG1 and mouse CD20 fused to human IgG Fc for making autoantibody to the Ig β , CD79 α , CD79 β and CD20 expressed by B cell, respectively.

The specification does not teach how to make and use *any* immunogenic composition mentioned above because a “first autologous polypeptide”, or “first autologous polypeptide which is immunologically cross-reactive with the undisclosed autologous polypeptide”, and “second heterologous polypeptide” without the amino acid sequence have no structure, much less function. Further, there is insufficient guidance as to which “portion” of the undisclosed first polypeptide that expressed on activated B cells that is immunogenic.

Stryer *et al*, of record, teach a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence and the corresponding nucleic acid sequence determines the conformational of the protein (See enclosed relevant pages).

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, *The Protein Folding Problem and Tertiary Structure Prediction*, pp. 492-495). Further, there are insufficient *in vivo* working examples demonstrating that any immunogenic composition comprising any undisclosed first autologous polypeptide, and any second heterologous polypeptide comprising T helper epitope is effective for eliciting *any* immune response against any “autologous antigen” in any subject such as human and nonhuman for treating autoimmune disease, or for targeted cells for elimination.

Even if the first autologous polypeptide is limited to Ig β , CD79 α , CD79 β and CD20 expressed by B cell, there is insufficient guidance as to which immune response against B cells in the subject that the claimed composition is being capable of eliciting.

Even if the composition is for antibody immune response, there is insufficient guidance and working example that the claimed immunogenic composition is effective for inducing autoantibody immune response against B cells or eliminating B cells in the subject because

Kuby *et al* teach that immunizing a peptide comprising a contiguous amino acid sequence of 8 amino acid residues or a protein derived from a full-length polypeptide may result in **antibody specificity** that differs from antibody specificity directed against the native full-length polypeptide. Given the indefinite number of undisclosed amino acids that can be added, it is

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unpredictable which undisclosed polypeptide would be useful for any purpose, especially for generating autoantibodies against a specific autoantigen to eliminate B cells in vivo.

Colman *et al* teach that even a single amino acid changes within the interface of an antibody-antigen can raise or lower the affinity of the antibody (See page 33, in particular).

Given the indefinite number of first autologous polypeptide, and second heterologous polypeptide, and the lack of guidance for the amino acid sequence of first autologous polypeptide and second heterologous polypeptide or which portion of which undisclosed first autologous polypeptide expressed on the surface of activated B cell, B cells or cells, which first polypeptide immunologically cross-reactive with the autologous polypeptide expressed on the surface of activated B cell, B cells or cells, it would take undue amount experimentation even for one skill in the art to practice the claimed invention.

Since the immunogenic composition comprising the "first autologous polypeptide", the immunologically cross-reactive autopolypeptide, and the second heterologous polypeptide is not enabled, it follows that any composition comprising said first and second polypeptides for eliciting any immune response against B cells such as autoantibody response, or targeting cells for elimination in a subject is not enabled. It also follows that the composition wherein the number or concentration of cells expressing the undisclosed first autologous polypeptide in the subject is reduced by at least about 35-40 % or 50% relative to prior treatment or in untreated subject is not enabled.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of *Ex parte Aggarwal*, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 8/22/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) the claims have been amended. The claims now require that that the first polypeptide be autologous to a subject or immunologically cross-reactive with the autologous polypeptide and that it be: i) an immunogenic portion of a polypeptide specifically

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expressed on the surface of activated B cells; ii) an immunogenic portion of a molecule selected from the group consisting of CD79 α , CD79 β , and CD20k iii) an immunogenic portion of polypeptide specifically expressed on the surface of cells targeted for elimination or reduction; or iv) an immunogenic portion of a polypeptide specifically expressed on the surface of B cells. (2) Applicants provide sufficient guidance such that one of ordinary skill in the art could practice the methods claimed in the claims without undue experimentation. For example, Applicants provide numerous examples of cell surface molecules that could be used to make the claimed immunogenic compositions. For example, the specification teaches that molecules such as TNFR, IL-4R, IL-12R, IL-2R, EGFR, PDGFR, bombesin receptor, CTLA4, CD3, membrane Ig, TCR, and Fc γ CD81, CD21, CD19, CD79, CD32, CD80, CD86, CD40, CD11a/CD18, CD22, CD45, CD28, CD2, CD4, CD8, CD154, CD54, CD43, CD45RO, CD64, CD46, CD56, and CD95, CD79a, CD79b, CD20, and CD19 can be used. (3) As required by the claims, the immunogenic composition must be capable of eliciting an immune response against an autologous polypeptide in the subject. (4) Applicants further argue that it is within the skill of the art to determine which first polypeptides would be useful and effective as part of a pharmaceutical composition based on their expression on a cell targeted for reduction or elimination. For example, many disorders or conditions were known in the art to be associated with B cells. For example, allergic disorders or autoimmune disorders involving antibody production. Similarly, other cell surface molecules are known in the art to be expressed on certain cells that it may be desirable to target for reduction or elimination, e.g., tumor cell surface molecules for reduction or elimination of cancer cells (e.g., molecules recognized by the Y2B8, Lym 1, Lym 2, LL2, Herz, B1, MBI, BH3, B4, 872.3, or 5E10 antibodies known in the art or immune cell surface molecules for reduction or elimination of immune cells to reduce unwanted or pathological immune response.

However, claims 3-4, 14, 15, 16, 19, 20, 39-40, 60, 61-62, and 68 still recite any first polypeptide be autologous to any subject such as human. Without the amino acid sequence of any first polypeptide be autologous to any subject such as human, one skill in the art cannot make, much less use the claimed invention for eliciting any immune response against B cells in the subject. Further, Given the indefinite number of first autologous polypeptide, and second heterologous polypeptide, and the lack of guidance for the amino acid sequence of first autologous polypeptide and second heterologous polypeptide or which portion of which undisclosed first autologous polypeptide expressed on the surface of activated B cell, B cells or cells, which first polypeptide immunologically cross-reactive with the autologous polypeptide

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expressed on the surface of activated B cell, B cells or cells, it would take undue amount experimentation even for one skill in the art to practice the claimed invention.

As for eliciting immune response, it is not clear which particular immune response the composition is eliciting against B cells. Even if it is limits to antibody response against B cells, not all B cells express the laundry list of polypeptide mentioned above, in turn, would be useful for eliciting antibody response against B cells in the subject, or reducing or eliminating the B cell population in the subject.

In response to cell surface molecules are known in the art, although cell surface molecules are known in the art, the specific molecules that are expressed on the specific cell population that are useful for eliciting autoimmune antibody response against the specific disease such as cancer required guidance. Further, there is insufficient in vivo working example demonstrating that any immunogenic composition comprising any undisclosed first autologous polypeptide or any first polypeptide immunologically cross-reactive with the undisclosed autologous polypeptide coupled to any heterologous polypeptide comprising T helper epitope is effective for eliciting any immune response against B cells, in turn useful for eliciting antibody response against B cells in the subject, or reducing or eliminating the B cell or any cell population in the subject for treating any disease such as cancer, or allergy. The fact that cells expresses more than one markers and other cells expressing the same markers as B cell, the immunogenic composition appears to lack the specificity for target for elimination or inducing autoimmune response in the absence of guidance. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, making and using the claimed composition for treating any disease would be unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

9. Claims 3-4, 14-17, 19-20, 26, 27, 30, 39-40, 60-62, 65, 67 and 68 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* immunogenic composition comprising *any* “first polypeptide” which is autologous to any subject or which is immunologically cross-reactive with the autologous polypeptide coupled to *any* “second polypeptide”, which is heterologous to the subject, wherein the first polypeptide

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comprises any immunogenic portion of any polypeptide specifically expressed on the surface of activated B cells and wherein the second polypeptide contains at least one T helper cell epitope, the composition being capable of eliciting any immune response against B cells in the subject,

(2) the immunogenic composition comprising *any* “first human polypeptide” which is autologous to the human subject or which is immunologically cross-reactive with the autologous polypeptide coupled to *any* “second polypeptide”, which is heterologous to the subject, wherein the first polypeptide comprises any immunogenic portion of any polypeptide specifically expressed on the surface of activated B cells and wherein the second polypeptide contains at least one T helper cell epitope, the composition being capable of eliciting any immune response against B cells in the subject,

(3) the immunogenic composition comprising *any* “first polypeptide” which is autologous to any subject or which is immunologically cross-reactive with the autologous polypeptide coupled to *any* “second polypeptide”, which is heterologous to the subject, wherein the first polypeptide comprises any immunogenic portion of any polypeptide specifically expressed on the surface of activated B cells and wherein the second polypeptide contains at least one T helper cell epitope, the composition being capable of eliciting any immune response against B cells in the subject wherein the first polypeptide and the second polypeptide are expressed as a fusion protein,

(4) The said immunogenic composition wherein the fusion protein is dimeric,

(5) The immunogenic composition comprising *any* “first polypeptide” which is autologous to any subject or which is immunologically cross-reactive with the autologous polypeptide coupled via a chemical linkage to *any* “second polypeptide”, which is heterologous to the subject, wherein the first polypeptide comprises any immunogenic portion of any polypeptide specifically expressed on the surface of activated B cells and wherein the second polypeptide contains at least one T helper cell epitope, the composition being capable of eliciting any immune response against B cells in the subject,

(6) *any* immunogenic composition comprising: a first polypeptide which is autologous to *any* subject or which is immunologically cross-reactive with the autologous polypeptide coupled to any second polypeptide which is heterologous to the subject, wherein the first polypeptide comprises *any* “immunogenic portion” of a molecule selected from the group consisting of: CD79 α , CD79 β , and CD20 and wherein the second polypeptide comprises at least

one T cell epitope, the composition being capable of eliciting any immune response against B cells in the subject,

(7) The composition comprising: a first human polypeptide which is autologous to human subject or which is immunologically cross-reactive with the autologous polypeptide coupled to any second polypeptide which is which is heterologous to the subject, wherein the first polypeptide comprises any "immunogenic portion" of a molecule selected from the group consisting of: CD79 α , CD79 β , and CD20 and wherein the second polypeptide comprises at least one T cell epitope, the composition being capable of eliciting any immune response against B cells in the subject,

(8) the composition comprising: a first human polypeptide which is autologous to human subject or which is immunologically cross-reactive with the autologous polypeptide coupled to any second polypeptide which is which is heterologous to the subject, wherein the first polypeptide comprises any "immunogenic portion" of a molecule selected from the group consisting of: CD79 α , CD79 β , and CD20 and wherein the second polypeptide comprises at least one T cell epitope, the composition being capable of eliciting any immune response against B cells in the subject wherein the first polypeptide and the second polypeptide are expressed as a fusion protein, a dimeric fusion protein, or coupled via a chemical linkage,

(9) The immunogenic compositions mentioned wherein the second polypeptide comprises at least a portion of an Fc region of an immunogenic molecule,

(10) *Any* immunogenic composition comprising any first polypeptide which is heterologous to any subject or which is immunologically cross-reactive with any autologous polypeptide to the subject coupled to any second polypeptide which is heterologous to the subject, wherein the first polypeptide comprises any immunogenic portion of any polypeptide specifically expressed on the surface of cells targeted for elimination or reduction and the second polypeptide comprises at least one T cell epitope and wherein the composition is capable of reducing or eliminating the cells expressing the cell surface receptor,

(11) The immunogenic composition comprising any first polypeptide which is heterologous to any subject or which is immunologically cross-reactive with any autologous polypeptide to the subject coupled to any second polypeptide which is heterologous to the subject, wherein the first polypeptide comprises any immunogenic portion of any polypeptide specifically expressed on the surface of cells targeted for elimination or reduction and the second polypeptide comprises at least one T cell epitope and wherein the composition is capable of

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reducing or eliminating the cells expressing the cell surface receptor wherein the first and the second polypeptides are expressed as a fusion protein or a dimeric fusion protein,

(12) The immunogenic composition comprising any first polypeptide which is heterologous to any subject or which is immunologically cross-reactive with any autologous polypeptide to the subject coupled to any second polypeptide which is heterologous to the subject, wherein the first polypeptide comprises any immunogenic portion of any polypeptide specifically expressed on the surface of cells targeted for elimination or reduction and the second polypeptide comprises at least one T cell epitope and wherein the composition is capable of reducing or eliminating the cells expressing the cell surface receptor wherein the second polypeptide comprises at least a portion of an Fc region of an immunoglobulin molecule,

(13) Any immunogenic composition comprising a first polypeptide which is autologous to any subject or which is immunologically cross-reactive with any autologous polypeptide coupled to any second polypeptide which is heterologous to the subject, wherein the first polypeptide comprises an immunogenic "portion" of any cell surface polypeptide specifically expressed on the surface of B cells and any second polypeptide comprises at least one T helper cell epitope, the composition being capable of eliciting any immune response against B cells in the subject,

(14) The immunogenic composition comprising a first polypeptide which is autologous to any subject or which is immunologically cross-reactive with any autologous polypeptide coupled to any second polypeptide which is heterologous to the subject, wherein the first polypeptide comprises an immunogenic "portion" of any cell surface polypeptide specifically expressed on the surface of B cells and any second polypeptide comprises at least one T helper cell epitope, the composition being capable of eliciting any immune response against B cells in the subject wherein the portion of non-human immunoglobulin molecule is derived from the Fc portion of the immunoglobulin,

(15) the immunogenic composition comprising a first polypeptide which is autologous to any subject or which is immunologically cross-reactive with any autologous polypeptide coupled to any second polypeptide which is heterologous to the subject, wherein the first polypeptide comprises an immunogenic "portion" of any cell surface polypeptide specifically expressed on the surface of B cells and any second polypeptide comprises at least one T helper cell epitope, the composition being capable of eliciting any immune response against B cells in the subject wherein the first polypeptide comprises the extracellular domain of any cell surface polypeptide,

(16) The compositions mentioned above wherein the number or concentration of cells expressing the polypeptide in the subject is reduced by at least about 35-40% or 50% relative to the number or concentration of cells prior to treatment or in an untreated subject, and

(17) the immunogenic composition mentioned above wherein the composition further comprises an adjuvant for treating any disease such as autoimmune disease.

The specification does not teach how to make and use *any* immunogenic composition comprising *any* “first polypeptide coupled to or fused to *any* “second polypeptide” heterologous to the subject because the terms “first polypeptide”, “second polypeptide” and “autologous antigen” without SEQ ID NO: do not convey any structure such as the amino acid sequence, much less about the function of said first and second polypeptides, as well as autologous antigen.

With the exception of the specific immunogenic composition comprising the specific autologous polypeptide coupled to the specific heterologous polypeptide for eliciting antibody response against B cells or eliminating B cells in the subject, there is inadequate written description about the structure associated with function of *any* first polypeptide which is heterologous to any subject, *any* first polypeptide which is immunologically cross-reactive with any autologous polypeptide to the subject, and any second polypeptide which is heterologous to the subject because the term “polypeptide” without the amino acid sequence has no structure, let alone function. Since the first polypeptide in the claimed composition is not adequately described, the polypeptide which is cross-reactive with said undisclosed first polypeptide is not described. Further, there is inadequate written description about which “portion” of the undisclosed first polypeptide is immunogenic for the claimed composition. Since

Since the immunogenic composition comprising the “first autologous polypeptide”, the immunologically cross-reactive autopolypeptide, and the second heterologous polypeptide is not adequately described, it follows that any composition comprising said first and second polypeptides for eliciting any immune response against B cells such as autoantibody response, or targeting cells for elimination in a subject is not sufficiently described. It also follows that the composition wherein the number or concentration of cells expressing the undisclosed first autologous polypeptide in the subject is reduced by at least about 35-40 % or 50% relative to prior treatment or in untreated subject is not adequately described. The specification discloses only Ig from human and mouse Ig β , CD79 α , CD79 β and CD20 expressed by B cell, given the lack of a written description of *any* additional representative species of “autologous polypeptide” expressed on activated B cell, or B cell or any cells in any subject, and “heterologous

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polypeptide” other than Fc of immunoglobulin, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co.* 43 USPQ2d 1398.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 “Written Description” Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

11. Claims 3-4, 14-17, 19-20, 26, 27, 30, 39-40, 60-62, 65, 67 and 68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3-4, 14-17, 19-20, 26, 27, 30, 39-40, 60-62, 65, 67 and 68 are indefinite in the recitation of “composition”. Minimally, a carrier should be recited, otherwise this reads as a compound per se.

The “number or concentration of cells expressing the polypeptide is reduced” in claims 61 and 62 has no antecedent basis in base claims 3 and 7 because base claim requires the immunogenic composition in claims 3 and 7 being capable of eliciting an immune response such as antibody response against B cells in the subject. Claims 61 and 62 should depend from claim 20.

The “portion of the non-human immunoglobulin molecule” in claim 40 has no antecedent basis in base claim 39 because said phrase is not recited in claim 39.

The “molecule” in claim 65 has no antecedent basis in base claim 20 because the word “molecule” is not recited in claim 20.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

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13. Claims 3, 4, 16-17, 20, 39, 61-62, 65, and 67 are rejected under 35 U.S.C. 102(b) as being anticipated by Eberl *et al* (Clin Exp Immunol 114: 173-178, Nov 1998; PTO 892).

Eberl *et al* teach an immunogenic composition comprising a first polypeptide such as anti-CD19 that is immunologically cross-reactive to autologous polypeptide CD19 and CD20 that expressed on the cell surface of B cell in a subject coupled or conjugated to second polypeptide that is heterologous to the subject comprising a T helper epitope such as P2 derived from tetanus toxin peptide (See entire document, abstract, page 173, column 2, in particular). The reference composition is capable of eliciting an immune response such as lysis or eliminating human B cell lymphoma by specific CD4 T cells for treatment of B cell lymphoma (See abstract, page 173, column 1, in particular). The reference first polypeptide and second polypeptide are coupled via a chemical linkage such as SPDP or sulfo-SMCC (See page 174, column 1, peptide-antibody conjugate, page 175, column 1, second paragraph, in particular). Claims 61-62 are included in this rejection because the reduction in number or concentration of cells expressing the reference polypeptide in the subject is an inherently properties of the reference composition. Thus, the reference teachings anticipate the claimed invention. Eberl *et al* teach that B cell can be "foreignized" by helper T epitope conjugate that directed against the common B cell marker and eliminated by the peptide specific T cells (See abstract, in particular). Thus, the reference teachings anticipate the claimed invention.

14. Claims 3, 4, 14, 19-20, 26-27, 30, 39, and 60 are rejected under 35 U.S.C. 102(b) as being anticipated by Lane *et al* (Immunology 80(1): 56-61, 1993; PTO 892).

Lane *et al* teach an immunogenic composition comprising a first polypeptide such as the extracellular portion of the mouse CTLA-4 that is autologous to the subject fused to a second polypeptide that is heterologous to the subject such as the constant region of human IgG1 (See abstract, in particular). The reference immunogenic composition is capable of eliciting an immune response such as inhibiting antigen presentation and induction of tolerance (See abstract, in particular). A product is a product irrespective of what its intended use. Claim 27 is included in this rejection because Fc region of IgG1 inherently capable of forming dimer because it contains cysteine residues. Thus, the reference teachings anticipate the claimed invention.

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15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

16. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).
17. Claims 17, 20, 65 and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eberl *et al* (Clin Exp Immunol 114: 173-178, Nov 1998; PTO 892) in view of Hashimoto *et al* (of record, Immunogenetics 40: 287-295, 1994; PTO 892) or Kooten *et al* (of record, Clin Exp Immunol 110: 509-515, 1997; PTO 892).

The teachings of Eberl *et al* have been discussed supra.

The claimed invention as recited in claims 17, 65 and 67 differs from the teachings of the reference only that the first polypeptide comprises at least a portion of a molecule selected from the group consisting of CD79 α , CD79 β and Ig.

Hashimoto *et al* teach a polypeptide such as human and mouse CD79 α (Ig- α /mb-1) that is a B cell-associated antigen that forms heterodimer with CD79 β to become a B cell surface receptor (See page 287, column 2, page 288, Figures 1&2, in particular). The reference polypeptide human CD79 α (Ig- α /mb-1) forming complex with CD79 β is critical for both cell surface expression and signaling functions of the B cell receptor (BCR) (See page 287, column 2, in particular).

Kooten *et al* teach that CD79 α (Ig- α /mb-1) and Ig- β (B29 or CD79 β) together form the B cell receptor and play a critical role in the development of B cells (See page 509, column 1, first paragraph, in particular). Kooten *et al* teach that that the same receptor can be used for

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negative selection processes to eliminate B cells with specificity for autoantigens (See page 510, column 1, first paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the anti-CD19 or CD20 as taught by Eberl *et al* for the CD79 α (Ig- α /mb-1) as taught by Hashimoto *et al* or the Ig- β (B29 or CD79 β) as taught by Kooten *et al* for an immunogenic composition comprising a first polypeptide which is a mouse CD79 α or CD79 β coupled to a second heterologous polypeptide such as T helper epitope derived from tetanus toxin for eliciting an immune response against B cells in the subject as taught by Eberl *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Hashimoto *et al* teach human CD79 α (Ig- α /mb-1) forming complex with CD79 β is critical for both cell surface expression and signaling functions of the B cell receptor (BCR) (See page 287, column 2, in particular). Kooten *et al* teach that that the CD79 α (Ig- α /mb-1) and Ig- β (B29 or CD79 β) B cell receptor can be used for negative selection processes to eliminate B cells with specificity for autoantigens (See page 510, column 1, first paragraph, in particular). Eberl *et al* teach that B cell can be "foreignized" by helper T epitope conjugate that directed against the common B cell marker and eliminated by the peptide specific T cells (See abstract, in particular).

18. Claims 3, 14, 15, 17, 20, 30, 65, and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lane *et al* (Immunology 80(1): 56-61, 1993; PTO 892) in view of US Pat 5,116,964 (May 1992; PTO 892) and Hashimoto *et al* (of record, Immunogenetics 40: 287-295, 1994; PTO 892) or Kooten *et al* (of record, Clin Exp Immunol 110: 509-515, 1997; PTO 892).

The teachings of Lane *et al* have been discussed supra.

The claimed invention as recited in claim 15 differs from the teachings of the reference only that the composition wherein the fusion protein is dimeric.

The claimed invention as recited in claims 17, 65 and 67 differs from the teachings of the reference only that the first polypeptide comprises at least a portion of a molecule selected from the group consisting of CD79 α , CD79 β and Ig.

The claimed invention as recited in claim 30 differs from the teachings of the reference only that composition wherein the second polypeptide comprises at least a portion of an Fc region of an immunoglobulin.

The '964 patent teaches fusion protein comprising the Fc region of the human immunoglobulin heavy chain or portion of the Fc region such as hinge, CH2, CH3 domain of IgG to human polypeptide expressing on the B cell such as gamma receptor (See entire document, column 10, lines 10-15, column 7, lines 49, in particular). The '964 patent teaches that the advantage of Fc fusion protein is that it extends the half-life of the fusion protein in circulation (See column 8, lines 10-36, in particular).

Hashimoto *et al* teach a polypeptide such as human and mouse CD79 α (Ig- α /mb-1) that is a B cell-associated antigen that forms heterodimer with CD79 β to become a B cell surface receptor (See page 287, column 2, page 288, Figures 1&2, in particular). The reference polypeptide human CD79 α (Ig- α /mb-1) forming complex with CD79 β is critical for both cell surface expression and signaling functions of the B cell receptor (BCR) (See page 287, column 2, in particular).

Kooten *et al* teach that CD79 α (Ig- α /mb-1) and Ig- β (B29 or CD79 β) together form the B cell receptor and play a critical role in the development of B cells (See page 509, column 1, first paragraph, in particular). Kooten *et al* teach that that the same receptor can be used for negative selection processes to eliminate B cells with specificity for autoantigens (See page 510, column 1, first paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the mouse CTLA-4 as taught by Lane *et al* for the mouse CD79 α (Ig- α /mb-1) as taught by Hashimoto *et al* or the Ig- β (B29 or CD79 β) as taught by Kooten *et al* for an immunogenic composition comprising a first autologous polypeptide which is a mouse CD79 α or CD79 β coupled to a second heterologous polypeptide such as human Fc as taught by Lane *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Hashimoto *et al* teach human CD79 α (Ig- α /mb-1) forming complex with CD79 β is critical for both cell surface expression and signaling functions of the B cell receptor (BCR) (See page 287, column 2, in particular). Kooten *et al* teach that that the CD79 α (Ig- α /mb-1) and Ig- β (B29 or CD79 β) B cell receptor can be used for negative selection processes to eliminate B cells with specificity for autoantigens (See page 510, column 1, first paragraph, in particular). The '964

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patent teaches that the advantage of Fc fusion protein is that it extends the half-life of the fusion protein in circulation (See column 8, lines 10-36, in particular).

19. Claim 40 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lane *et al* (Immunology 80(1): 56-61, 1993; PTO 892) in view of Hashimoto *et al* (Immunogenetics 40: 287-295, 1994; PTO 892) or Kooten *et al* (Clin Exp Immunol 110: 509-515, 1997; PTO 892) as applied to claims 3, 14, 15, 17, 20, 30, 65, and 67 and further in view of Isaacs *et al* (British J of Rheumatology 36: 305-309, 1997; PTO 892).

The combined teachings of Lane *et al*, the '964 patent, Hashimoto *et al* and Kooten *et al* have been discussed supra.

The claimed invention in claim 40 differs from the combined teachings of the references only that the composition wherein the immunoglobulin molecule is derived from the non-human Fc portion of the immunoglobulin.

Isaacs *et al* teach various fusion proteins such as extracellular domain of CD4 molecule fused to the part of immunoglobulin such as the hinge, CH2 and CH3 domains or CTLA4-Ig (see page 305, in particular). Isaacs *et al* teach that the Fc region of the immunoglobulin endows the fusion protein with specific properties such as prolonged the circulating half life, enabled dimerization thereby increasing avidity for the ligand and it provides effector function such as opsonization by Ig for enhanced phagocytosis or complement mediated lysis (See page 305, column 1, in particular). However, Isaacs *et al* teach that because their sequences such as CD4 and Fc are derived from self-proteins, they are less immunogenic (See page 305, second paragraph, in particular). From the teaching of the Isaacs *et al* as discussed supra, it is apparent that one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in producing the claimed invention by substituting the human Fc from self as taught by the Lane *et al* or Isaacs *et al* for the non-self Fc portion of the immunoglobulin such as non-human Fc because proteins derived from self-protein is less immunogenic as taught by Isaacs *et al*.

One having ordinary skill in the art would have been motivated to do this because Isaacs *et al* teach that the Fc region of the immunoglobulin endows the fusion protein with specific properties such as prolonged the circulating half life, enabled dimerization thereby increasing avidity for the ligand and it provides effector function such as opsonization by Ig for enhanced

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phagocytosis or complement mediated lysis and non-self protein is more immunogenic (See page 305, column 1, in particular)

20. Claim 68 is rejected under 35 U.S.C. 103(a) as being unpatentable over Eberl *et al* (Clin Exp Immunol 114: 173-178, Nov 1998; PTO 892) in view of Harlow et al in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 98-99).

The teachings of Eberl et al have been discussed supra.

The claimed invention as recited in claim 68 differs from the teachings of the reference only that composition further comprises an adjuvant.

Harlow et al teach various adjuvants such as Freund's adjuvant, aluminum hydroxide or heat killed B pertussis for stimulating and prolonging the immune responses such as antibody immune response to soluble antigens (See page 98-99, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include adjuvant as taught by Harlow et al in any immunogenic composition such as anti-CD19 that is immunologically cross-reactive to autologous polypeptide CD19 and CD20 that expressed on the cell surface of B cell in a subject conjugated to second polypeptide that is heterologous to the subject comprising a T helper epitope such as P2 derived from tetanus toxin peptide as taught by Eberl *et al* (See entire document, abstract, page 173, column 2, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Harlow et al teach that adjuvant stimulates and prolongs the immune responses such as antibody immune response to soluble antigens (See page 98-99, in particular).

21. Claim 68 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lane *et al* (Immunology 80(1): 56-61, 1993; PTO 892) in view of Harlow et al Harlow et al (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 98-99).

The teachings of Lane et al have been discussed supra.

The claimed invention as recited in claim 68 differs from the teachings of the reference only that composition further comprises an adjuvant.

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Harlow et al teach various adjuvants such as Freund's adjuvant, aluminum hydroxide or heat killed B pertussis for stimulating and prolonging the immune responses such as antibody immune response to soluble antigens (See page 98-99, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include adjuvant as taught by Harlow et al in any immunogenic composition such as the extracellular portion of the mouse CTLA-4 that is autologous to the subject fused to a second polypeptide that is heterologous to the subject such as the constant region of human IgG1 as taught by Lane *et al* (See abstract, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Harlow et al teach that adjuvant stimulates and prolongs the immune responses such as antibody immune response to soluble antigens (See page 98-99, in particular).

22. No claim is allowed.
23. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are

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unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

25. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.

Patent Examiner

Technology Center 1600

November 26, 2003


CHRISTINA CHAN
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